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Global Emerging HEmophilia Panel (GEHEP): A Multinational Collaboration for Advancing Hemophilia Research and Treatment

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Summary

GEHEP, established in 2009, is an independent, multi-institutional, international consortium of early career hematology specialists in the field of hemophilia and other inherited bleeding disorders. The main objective of the group, whose members practice at institutions in North America, Europe, and South Africa, is to advance hemophilia care by providing a forum for mentored collaborative research, developing programs for improving clinical care, and promoting academic career development of junior faculty. GEHEP members collect and document anonymized data on intra- and interinstitutional differences in patient populations, diagnosis, and treatment in the field of hemophilia and other bleeding disorders. To facilitate sharing of aggregated data among GEHEP members, a global protocol was developed and approved by most members' local institutional review board. Current GEHEP research initiatives are varied, encompassing work in pediatric and adult patients. GEHEP members have presented research at international meetings on the initiation of prophylaxis in children, use of immune tolerance induction in adults, and prevalence of acute coronary syndromes in older patients with hemophilia. The main goal of the continuing work of GEHEP is to advance the care of patients with hemophilia worldwide.

Introduction

Hemophilia A and B are inherited bleeding disorders resulting from a deficiency of clotting factor VIII and factor IX, respectively [1]. As X-linked disorders, both types of hemophilia occur almost exclusively in boys, with an incidence of 1 in 5,000 male births for hemophilia A and 1 in 25,000 male births for hemophilia B [1]. Hemophilia severity is defined by the level of clotting factor present in blood (severe <1% of normal levels; moderate 1–5%; mild >5 to <40%) [2]. Patients with mild hemophilia typically experience excessive bleeding only after serious injury, trauma, or surgery; those with mod-

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erate hemophilia bleed excessively after injury but also sometimes spontaneously. In patients with severe hemophilia, spontaneous bleeding episodes are common, particularly into muscles and joints [3]. No ethnic or geographic predisposition to hemophilia has been identified [1], but geographic differences are seen in diagnosis, treatment approaches, and access to treatment. Particularly in developing countries, hemophilia is underdiagnosed and undertreated [4].

Bleeding episodes in patients with hemophilia are treated or prevented by infusion of the deficient clotting factor, using either plasma-derived or recombinant factor replacement products. Optimal care of patients with hemophilia requires a comprehensive approach delivered by a multidisciplinary team of specialists [5]. This specialized care, which encompasses the medical and psychological aspects of hemophilia, is generally delivered in a dedicated hemophilia treatment center [5]. Typically, these specialized clinics also provide care for patients with other inherited bleeding disorders, including von Willebrand disease, other coagulation factor deficiencies, and platelet disorders.

Despite advances in the management of hemophilia and other bleeding disorders, access to specialized centers and comprehensive care, coupled with a shortage of physicians trained in the management of hemostasis and thrombosis, remains a challenge. Attrition of specialized healthcare providers and senior clinicians threatens the existence of some hemophilia treatment centers [6]. The Global Emerging HEmophilia Panel (GEHEP) was established in 2009 to address some of the workforce challenges and to create a consortium of junior faculty to foster collaborative research that benefits patients and is a vital component for the success of academic faculty. Thus, in addition to improving clinical practice internationally, GEHEP enhances career development by providing research opportunities and encouraging collaboration among contemporaries. Mentorship for GEHEP members is currently provided by 2 senior researchers in the field of hemophilia and inherited bleeding disorders: Dr. Gerry Dolan (Nottingham University Hospitals, Nottingham, UK) and Dr. Roshni Kulkarni (Michigan State University, East Lansing, MI, USA). Before joining the National Heart, Lung, and Blood Institute (Bethesda, MD, USA), Dr. Donna DiMichele had served as a GEHEP mentor. Administrative and meeting support for GEHEP is provided by Bayer HealthCare.

Global Emerging HEmophilia Panel

GEHEP is an independent, multi-institutional, international consortium of physicians who manage both pediatric and adult patients with hemophilia or other inherited bleeding disorders. The objective of the group is to advance patient care by providing a forum for multinational collaborative research by emerging leaders in the field of hemostasis, facilitated by mentors. Current GEHEP members practice at treatment centers, primarily academic institutions, in Canada, Germany, Italy, Norway, South Africa, Spain, the UK, and the USA.

Because diagnostic methods, treatment approaches, and management of age-related comorbidities vary among study centers, a principal aim of GEHEP is to document and study intra- and interinstitutional differences in patient populations, diagnosis, and treatment to provide a basis for identifying future areas of research. All GEHEP projects are reviewed and approved by the local institutional review board (IRB) of each member. Information included in the GEHEP project databases is collected through written or electronic surveys approved and completed by all GEHEP members. Many of the participating treatment centers maintain local databases of clinical data, which are accessed to provide information about the patient population of interest. In cases in which specific information is required, patient medical records are reviewed, and only anonymized patient data are included in the database. For example, patient name, address, birth date, admission and discharge dates, social security number, medical record number, full-face photograph, or any other unique identifying data are not collected.

Data collected in the GEHEP databases, which are project-specific and maintained at the project leader's institution, include demographic data, number of patients at each center with hemophilia A or hemophilia B, and disease severity. In addition, more specific data are collected as required by the many ongoing or completed GEHEP-independent research projects. Examples of such data include treatment provided in various settings (e.g., management of acute coronary syndromes or patients undergoing orthopedic surgery), results and complications of treatment, and comorbidities. Data collection has also included the types of laboratory tests available at each center for evaluation of patients experiencing bleeding episodes and the general practices or guidelines followed in specific clinical situations. The databases are accessible only by GEHEP members, and all data analyses are performed by GEHEP.

Research Initiatives

Members of GEHEP meet annually to discuss current and future research initiatives. Additional meetings are held in conjunction with major international hematology congresses, such as those of the American Society of Hematology, the International Society on Thrombosis and Haemostasis (ISTH), and the World Federation of Hemophilia (WFH). Invited lectures at some of these meetings by experts in the field of study design and public health further assist in the critical thinking process.

These initiatives encompass a range of research interests, all of which are designed to bring an international perspective to advancing patient care. To facilitate this, a key overall goal of GEHEP was to develop a single global protocol approved

Table 1. Summary of GEHEP research presentations

Authors	Title	Key points	Congress
Bidlingmaier et al. [7]	Technical issues in implementing prophylaxis in children with hemophilia: an international survey	• When and how to start prophylaxis varies among centers • Protocols for dosing, preventing complications, and use of central venous access devices are not standardized across centers	World Federation of Hemophilia; July 8–12, 2012; Paris, France
Fogarty et al. [8]	Presentation and management of acute coronary syndromes (ACS) among adult persons with hemophilia (PWH): results of an international, retrospective, 10-year survey	• Ischemic heart disease may be more common among younger patients with hemophilia than previously reported • All patients with hemophilia, including younger patients with few risk factors, should be screened for ischemic heart disease and preventive strategies implemented	Scientific and Standardization Committee of the ISTH; June 27–30, 2012; Liverpool, UK
Holme et a.l [9]	Variations in international practices for the peri-operative management of major surgery for persons with severe hemophilia	• Use of antifibrinolytic agents and thromboprophylaxis varies in the perioperative management of patients with severe hemophilia	World Federation of Hemophilia; July 10–14, 2010; Buenos Aires, Argentina
Kruse-Jarres et al. [10]	Inhibitor eradication practices in adult patients – results of a global survey	• Management of patients with inhibitors is fairly uniform across geographically diverse GEHEP centers	World Federation of Hemophilia; July 10–14, 2010; Buenos Aires, Argentina
Chitlur et al. [11]	International survey of laboratory tests used in the diagnosis and evaluation of hemophilia A	• All laboratory tests used in the diagnosis and classification of FVIII deficiency have limitations • Physicians need to keep these limitations in mind when interpreting test results	World Federation of Hemophilia; July 10–14, 2010; Buenos Aires, Argentina

FVIII = factor VIII

by each GEHEP member's IRB to promote sharing of anonymized aggregated data. Almost all participating centers had the global protocol approved by their respective institutions within the first 2 years of the group's inception.

Global Protocol

The objective of the global protocol is to provide an umbrella protocol under which a number of research projects can be initiated, thereby streamlining the IRB process. The specific goal is to collect and document intra- and interinstitutional anonymized data from each GEHEP center on the diagnosis and management of hemophilia and hemophilic complications in children and adults and of diseases of aging in the hemophilic population.

Because of interinstitutional differences in IRB requirements, the global protocol was submitted and approved by most, but not all, GEHEP centers. At centers that have not approved the global protocol, specific project protocols are submitted and approved on an individual basis.

Current Research

Research by GEHEP members that has been presented at hematology congresses is summarized in table 1. Research efforts currently in progress in pediatric patients include a study of the initiation of prophylaxis in children with hemophilia A or hemophilia B. This study focuses on criteria used to start prophylaxis, choice of factor replacement product, treatment regimen and dosage, inhibitor prevalence, rate of breakthrough bleeding, and central venous line use. Results from this study, describing the technical aspects of implementing prophylaxis in children, were presented at the WFH congress held in Paris, France, in July 2012 [7].

Research in adults includes a study on acute coronary syndromes that drew from a 10-year retrospective database. Results from this study were presented at the Scientific and Standardization Committee meeting of the ISTH held in Liverpool, UK, in June 2012 [8]. A future study has been proposed to gather data on the incidence and management of stroke and atrial fibrillation in patients with hemophilia or other bleeding disorders.

Another study in adult patients explored GEHEP member practices regarding management of patients with severe hemophilia undergoing orthopedic or other surgery. Results from this study were presented at the WFH congress held in Buenos Aires, Argentina, in July 2010 [9]. A proposal has been made to capture additional retrospective data from this patient population, including further data on the use of thromboprophylaxis, over a 5-year period.

Members of GEHEP have undertaken a two-part research initiative on immune tolerance induction (ITI). The first part of this project was a survey on inhibitor eradication practices in adults. Survey results were presented at the 2010 WFH congress [10]; a follow-up survey is being conducted to further explore ITI use in adults. The second ITI initiative is a regis-

try to collect data on rituximab use in pediatric and adult patients with inhibitors.

Data also have been gathered by GEHEP to determine the types of laboratory assessments used to diagnose hemophilia A. This work, which was presented at the WFH congress in 2010 [11], focuses on differences in GEHEP member practices regarding types of assays used and genotyping.

Future Research

Through the unique prism of this international collaboration, GEHEP research data have improved our understanding of the challenges of caring for patients with hemophilia or other inherited bleeding disorders. Future GEHEP areas of interest include female carriers, mild hemophilia, mucocutaneous bleeding, and vaccination practices. Innovative, new prospective studies will be shaped by retrospective data collection.

Conclusions

GEHEP is a successful multinational collaboration of specialists whose goal is to advance research in and treatment of hemophilia and other inherited bleeding disorders. Development of a global protocol, approved by each GEHEP member's IRB, facilitates sharing of anonymized aggregated data. Collection and documentation of intra- and interinstitutional de-identified data provides a foundation on which to base future priorities for clinical care and research. Presentations of GEHEP research at national and international meetings contribute to the scientific knowledge base, support the career development of young investigators, and help promote and sustain an adequate workforce in the field of bleeding disorders. These efforts need to be expanded to include investigators from developing countries.

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